Op-Ed

The male menopause: does it exist?

FOR: Some men need investigation and testosterone treatment see opposing view p. 78

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The term "male menopause" is inappropriate because it suggests a sudden drop in sex hormones such as occurs in women in the perimenopausal state. It is not an inevitability but may occur mainly in middle-aged and elderly men when testosterone production and plasma concentrations fall. A threshold of plasma concentrations seems to exist, below which symptoms may become apparent. Testosterone concentrations found to be critical for sexual functioning in men lie around 10.4 nmol/L (300 ng/dL), although they vary among individuals.[1] Although some have found that differences in plasma testosterone concentrations within the normal range in young healthy men do not correlate with differences in sexual activity and interest, others have shown that differences in the concentrations of the potent metabolite, dihydrotestosterone, do.[2,3]

Earlier this century, the term "male climacteric" (from the Greek *klimacter*, the rung of a ladder) was used and is more appropriate because it suggests a decline and not a precipitous drop in hormone concentrations.[4,5] A landmark paper of 1944 accurately described symptoms, reversed by testosterone replacement but not by placebo, seen in men suffering from an age-associated decline in testosterone concentrations.[5] Because of the similarity of most of the symptoms between men and women, the term "menopause" gained popularity and has, unfortunately, stuck.

An abnormally low concentration of testosterone (hypotestosteronemia) may occur because of testicular dysfunction (primary hypogonadism) or hypothalamic-pituitary dysfunction (secondary hypogonadism) and may be congenital or acquired.

ENDOCRINOLOGY

In aging men, a reduction in testosterone concentration is due mainly to a decline in Leydig cell mass in the testicles or a dysfunction in hypothalamic-pituitary homeostatic control, or both, leading to abnormally low secretion of luteinizing hormone with resultant low testosterone production. It is well recognized that with normal male aging, mean plasma testosterone concentrations decline, albeit with considerable variability between men and with a broad range in age-related values. Cross-sectional and prospective studies show a decline that starts in early middle age and then progresses in a linear fashion.[6-11] Mirroring this decline in plasma testosterone concentration is an age-associated increase in plasma concentration of sex hormone–binding globulin (SHBG), resulting in a more pronounced decline in the active or bioavailable testosterone moiety.[12-14] Concentrations of bioavailable testosterone decrease by as much as 50% between the ages of 25 and 75 years,[15] and it has been proposed that with respect to bioavailable concentrations, as many as 50% of men older than 50 years are hypotestosteronemic when compared with peak early morning concentrations in young men.[16] With age, a loss of hypothalamopituitary circadian rhythm occurs, which may result in exaggerated falls in plasma testosterone concentrations by evening.

Symptoms of the male climacteric syndrome*

- Depression, nervousness
- Flushes and sweats
- Decreased libido
- Erectile dysfunction
- Easily fatigued
- Poor concentration and memory

*From Heller and Myers[5]

Malcolm Willett

EFFECTS OF HYPOTESTOSTERONEMIA

A quantitative definition of hypotestosteronemia has generally been accepted as 11 nmol/L (320 ng/dL) because only 1% of healthy men aged 20 to 40 years will have a concentration below this limit.[17] The development of hypotestosteronemia may be related to heredity because 60% of the variability of testosterone concentrations and 30% of that of SHBG may be due to genetic factors.[18] A his-

tory of orchitis, testicular trauma, or other pathologic disorder may be contributory. The presence of obesity is associated with lower concentrations of bioavailable testosterone,[19] and insulin concentrations have been found to be indirectly correlated with SHBG and testosterone concentrations.[20] With respect to lifestyle, excess intake of alcohol and physical and psychological stress are all associated with lowered testosterone concentrations.[21,22]

Aging is usually associated with a decline in sexual interest and potency.[23] This suggests that such changes in sexual behavior are androgen-dependent but does not prove the case. Although erectile dysfunction in elderly men is often of nonhormonal cause, testosterone deficiency accounts for 6% to 45% of all cases.[24]

Affective symptoms have long been associated with hypotestosteronemia: depressed mood is significantly correlated with low concentrations of bioavailable testosterone in older men.[14] Some longitudinal uncontrolled studies of hypotestosteronemic men have shown that symptoms of depression, anger, irritability, sadness, and nervousness significantly decreased and friendliness, a sense of well-being, and energy levels improved with androgen treatment.[25,26] Evidence suggests that mood disturbance may be linked to hypotestosteronemia and that testosterone replacement therapy may be beneficial, but placebo-controlled trials are needed to confirm these issues. Fatigue may occur with hypotestosteronemia. During one prospective study, symptoms significantly lessened with supplementation and increased during androgen withdrawal; another showed substantially improved energy levels.[26]

Male aging is associated with an increase in central and upper body fat deposition and reduced muscle mass and strength. This could be explained by an age-associated decline in growth hormone concentrations, which itself is associated with an increase in SHBG and, therefore, a reduction in bioavailable testosterone.[27] The consensus is that testosterone supplementation in hypotestosteronemic men enhances fat-free mass, muscle bulk, and strength.[28,29] Profound hypotestosteronemia in younger men results in accelerated bone loss and osteoporosis.[30] In older men, bioavailable testosterone concentrations are positively correlated with bone mineral density at the radius, spine, and hip,[31] and men with hypotestosteronemia have been reported to be at increased risk of hip fracture.[32] Data on the effects of testosterone replacement therapy on bone metabolism in hypotestosteronemic men are limited but suggest benefit.[33]

Vasomotor disturbance and night sweats occasionally occur, their association with testosterone deficiency and relief by testosterone replacement being noted as far back as the 1930s.[4,5,34] Androgens also have an important role in the development of cognitive functioning, and in men, strong correlations exist between testosterone concentrations and visuospatial abilities in certain domains.[35] Testosterone administration to aging men has been shown to enhance certain visuospatial skills.[36]

Hypogonadism (like hypothyroidism) is a pathologic state and is associated with several other comorbid factors, such as the presence of cardiovascular risk factors (obesity, higher waist:hip ratio; higher concentrations of glucose, insulin, total cholesterol, low-density-lipoprotein cholesterol triglycerides, apolipoprotein B, fibrinogen, and plasminogen activator inhibitor I; and lower concentrations of high-density-lipoprotein cholesterol C and apolipoprotein A-I), which are improved by testosterone administration.[37]

INVESTIGATIONS AND TREATMENT

Whatever the nomenclature, be it male menopause or climacteric or age-related hypotestosteronemia, an investigation should be undertaken for men presenting with symptoms outlined in the box. This should include an assessment of concentrations of plasma gonadotropin, prolactin, and SHBG and early morning concentrations of testosterone. Men with hypotestosteronemia with unequivocal signs and symptoms of androgen deficiency, and when reversible causes of testosterone deficiency and contraindications have been excluded, should be offered treatment with testosterone replacement therapy in line with the current World Health Organization guidelines.[38] This, however, is a specialty beyond the scope of this article.

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